REMARKS

Applicant thanks the Examiner for the opportunity to correct the inadvertent errors. Applicant has provided a complete listing of all claims properly labeled in accordance with 37 C.F.R. §1.121(c). Applicant has relabeled claims 23 and 31 "withdrawn" as requested by Examiner.

Applicant respectfully requests continued examination of the present patent application pursuant to 37 C.F.R. § 1.114, and entrance on the record of the Declaration of Hans Klingemann, M.D., Ph.D., pursuant to 37 C.F.R. § 1.132 (hereinafter, "Klingemann Decl.") in further support of lack of obviousness that is attached in Appendix A hereto and incorporated herein.

The Final Office Action has been carefully considered. Applicants respectfully traverse the Examiner's basis therein for rejecting the claimed invention because the Gong et al. reference in view of Santoli et al. do not teach or suggest Applicant's claimed invention for at least the reasons explained below and those previously submitted in the Amendment and Response dated October 5, 2007 ("the "Initial Response"), which response is incorporated as if set forth entirely herein. Accordingly, Applicant respectfully requests the Examiner reconsider the application in view of the claim rejection, and issue a notice of allowance.

I. Status of Claims

Claims 1-31 are pending. Claims 1-19, 21, 23, 24, 25, 28, 29, and 31 were previously withdrawn from consideration in response to election requests pursuant to 35 U.S.C. § 121 and rights were reserved to subsequently prosecute the withdrawn subject matter. Claims 20, 22, 26, 27 and 30 are currently rejected in the Final Office Action mailed on April 15, 2008.

II. Double Patenting

The Examiner has provisionally rejected claims 20, 22, 26, 27 and 30 under the nonstatutory judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-35, 46, 48, 50 and 53 of copending Application No. 10/701,359. on grounds that although the conflicting claims are not identical, they are not patentably distinct from each other. Applicants will file a terminal disclaimer to overcome the double patenting rejection, upon indication of allowable subject matter.

III. Claim Rejections

A. Section 112 – Second Paragraph

Applicant appreciates the Examiner's withdrawal of the prior rejection of claims 20, 22, 26, 27 and 30 based on Section 112, second paragraph.

B. Section 103(a)

The Examiner has maintained the rejection of claims 20, 22, 26, 27 and 30 pursuant to 35 U.S.C. § 103(a) as being unpatentable over Gong et al., *Leukemia* 8:652-658, 1994 ("Gong et al.") in view of U.S. Patent No. 5,272,082 to Santoli et al. ("Santoli et al.") on grounds that "It would have been prima facie obvious … to have created the claimed invention because Gong et al. teach use of NK-92 cells, while Santoli et al. teach *in vivo* use of cytotoxic cell lines. One of ordinary skill in the art would have been motivated to do so because Santoli et al. teach that lytic human derived cell lines can be used in vivo to treat disease or in preclinical in vivo studies (see column 10)." Final Office Action, ¶ 10. Applicants respectfully traverse the rejection because although Santoli et al. disclose that T-ALL cells can be used *in vivo* that disclosure would not suggest the claimed method.

Gong et al. established the existence of NK-92 cells and set out to characterize the NK-92 cell line for use as a research tool. Santoli et al. teach "genetically modified cytotoxic T

lymphoblastic leukemia cell lines (T-ALL), and uses of these cell lines in cancer therapy" (Santoli et al., Abstract), not NK-92 cells or methods of the present invention. Rather, Santoli et al. disclose specifically the T-ALL cell lines 104, 107 and 103/2 and their use to treat cancer, both *in vivo* and *ex vivo* (10:30-60). T-ALL cells are not even comparable or related to the NK-92 cell line developed and disclosed in Gong et al. Klingemann Decl., ¶ 28. Examples of the phenotypic and functional differences were set out in the Initial Response and are further supported by the Declaration of Hans Klingemann. Because of these differences, there would have been no reason apparent to one skilled in the art at the time the claimed invention to look to Santoli et al.'s teaching of T-ALL cells for any teaching with respect to a method of treating a pathology *in vivo* in a mammal by administering NK-92 cells claimed by Applicant. Klingemann Decl., ¶ 27-34. Furthermore, if there is a teaching, suggestion, or incentive, it must motivate the skilled artisan to combine the teachings or suggestions with a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art. See In re Vaeck, 947 F.2d 488; M.P.E.P. § 2143.03. Because of the distinctive differences between the cell lines, one skilled in the art would not have had a reasonable expectation of success. The usefulness and necessary requirements for each would have to be characterized independently. Klingemann Decl., ¶ 29.

The Examiner has acknowledged the "two types of cells differ in phenotype" but has still concluded that "both the cells described by Santoli et al. and NK-92 are lytic human derived cell lines that can lyse various tumor cells." Final Office Action, ¶ 10. This conclusion is inaccurate because Gong et al. do not teach that NK-92 cells are capable of lysing various tumor cells of different origin or type. Klingemann Decl., ¶ 24. Instead, Gong et al. teach that NK-92 cells

demonstrated cytotoxicity against two human leukemic cell lines in studies developed to characterize the newly isolated cell line. Further, given the significant phenotypic and functional differences between NK-92 cells and T-ALL cells, there would not have been any reason apparent to one skilled in the art at the time the claimed method was developed to look to Santoli et al.'s teaching of T-ALL cells to arrive at a method of treating a pathology *in vivo* in a mammal by administering NK-92 cells. Klingemann Decl., ¶ 29. Thus, contrary to the Examiner's conclusion, because Gong et al. do not teach that technique it could not be obvious to use it to arrive at let alone improve another technique.

Quoting KSR Int'l Co. v. Teleflex Inc., 550 U.S. m. 2007 WL 1237837 at 13 (2007), the Examiner states "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." The Examiner has acknowledged that the two types of cells differ in phenotype. One skilled in the art would appreciate the distinguishing characteristics of these two cell lines, or any cell line. Klingemann Decl., ¶ 27. Santoli et al only teach methods applicable to T-ALL cells and do not provide guidance as to any other cell lines. Gong et al. identify and partially characterize NK-92 cells, which at the time was a new cell line. These two cell lines are from different cell lineages derived from different disease categories, leukemia and lymphoma. The T-ALL cell lines were derived from a patient with ALL, whereas the NK-92 cell line was derived from a patient with an aggressive LGL lymphoma. Klingemann Decl., ¶ 28. The actual application of a method for treating a pathology *in vitro* in a mammal by administering NK-92 cells would not have been obvious to a person of ordinary skill in the art based on the methods and teachings disclosed in Santoli et al. Klingemann Decl., ¶ 29 and 30. The phenotypic and functional differences

between the cells inherently prevent the know-how from one to be automatically transferred to the other, especially with any expectation of success.

The Examiner further noted "[r]egarding applicants' comments about Gong et al., there is no teaching in Gong et al. that NK-92 cells are unacceptable for in vivo use." Final Office Action, ¶ 10. That notation, however, is irrelevant. Gong et al. do not teach or suggest that the NK-92 cells disclosed therein *could* be used *in vivo* to lyse tumor cells. Klingemann Decl., ¶ 24. It is the teaching of the reference that is relevant to an obviousness analysis, not what the reference does not teach. *See, e.g.,* M.P.E.P. § 2143.01, citing *KSR Int'l v. Teleflex Inc.*, 127 S.Ct. 1727, 1740-1741 (2007) (stating that "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness").

Further, Applicant disagrees with the Examiner's conclusion that "NK-92 cells could be used in patients that contained tumor cells that were not lysed by T-ALL cells." Final Office Action, ¶ 10. This conclusion is irrelevant to the claims at issue in this application. The method of using NK-92 cells as a treatment *in vivo* is very different from using T-ALL cells because the cells are phenotypically and functionally very different. Each must be evaluated independently. Klingemann Decl., ¶ 27.

Comparative studies of NK-92 cells and TALL-104 cells demonstrate that these cell lines are functionally quite different, with NK-92 cells having significantly higher cytotoxic activity than TALL-104 cells. For example, many hematological cancers are susceptible to killing by NK-92 cells, whereas these cancers are mostly resistant to lysis by TALL-104 cells. Klingemann Decl., ¶ 31. In fact, data disclosed in the '955 Application demonstrate that NK-92 cells are

more cytolytic than TALL-104 or YT cells. *See* '955 Application, Tables 5 and 6, Fig. 9. Klingemann Decl., ¶ 32.

Notably, the results demonstrating that the NK-92 cell line is a superior cell line to the TALL-104 cell line were surprising. Klingemann Decl., ¶ 33. Successful results and evidence of discovery further establish the patentability of Applicant's claimed modified NK-92 cells. "[O]bjective evidence such as commercial success, failure of others, long-felt need, and unexpected results must be considered before a conclusion on obviousness is reached." *Minnesota Mining & Manufacturing Co. v. Johnson & Johnson Orthopedics, Inc.*, 976 F.2d 1559, 1573 (Fed. Cir. 1992) (noting the importance of secondary considerations in the obviousness analysis), citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802, F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986). Recent clinical trial studies demonstrated the "feasibility of large-scale expansion and safety of administering NK-92 cells as allogeneic cellular immunotherapy in advanced cancer patients and serves as a platform for future study of this novel natural killer (NK)-cell based therapy." (Cytotherapy 10(6): 625-632, 2008). The methods used were tailored to NK-92 cells, which are very different from the methods tailored to T-ALL cells. Klingemann Decl., ¶ 35.

For at least these reasons, one skilled in the art of tumor immunology would not have combined Gong et al. with Santoli et al. at the time of Applicant's invention to arrive at the claimed method of treating a pathology *in vivo* in a mammal by administering a medium comprising NK-92 cells.

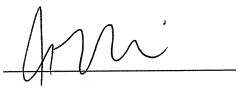
IV. Conclusion

Applicant respectfully submits that the application and claims are in condition for allowance. Accordingly, reconsideration and allowance of all claims are respectfully requested.

Applicant would appreciate the courtesy of a telephone call should the Examiner have any questions or comments with respect to this response or the claim language for purposes of efficiently resolving same.

The Commissioner is hereby authorized to charge Deposit Account No. 03-2026 for any fees associated with this Request for Continued Examination.

Respectfully submitted,

By 

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